

# “Value” of improved treadmill exercise capacity: lessons from a study of rate responsive pacing

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## Abstract

**Objectives**—To compare the value of a series of cardiovascular measurements in patients with symptomatic disease receiving an effective treatment (rate responsive pacing).

**Patients**—12 pacemaker dependent patients with VVIR units.

**Interventions**—Single blind crossover between VVI and VVIR.

**Outcome measures**—Exercise capacity was assessed by treadmill tests (modified Bruce protocol and a fixed workload protocol) with respiratory gas analysis. Self paced corridor walk tests were also undertaken. Quality of life (QOL) was assessed by questionnaire. Daily activity was measured in the patients' homes using shoe and belt pedometers.

**Results**—Treadmill tests and QOL questionnaires correctly identified the clinical benefit associated with VVIR. The modified Bruce protocol was superior to the fixed workload protocol as it was better tailored to the fairly well preserved exercise capacity of the patients. Symptom scores, but not walking times, were improved with VVIR during corridor walk tests. VVIR did not improve daily activity measured using either the belt or shoe pedometers.

**Conclusions**—VVIR pacing improved some but not all measures of exercise capacity. This finding illustrates the difficulty of selecting an instrument to measure symptomatic improvement in clinical research; and raises the question, what is the best way of measuring exercise capacity?

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Keywords: rate responsive pacing; exercise capacity; quality of life

The evidence in favour of rate responsive pacing is indisputable. Rate responsive pacing can be used as a tool to compare the usefulness of cardiovascular tests for detecting improvements in clinical status.

Exercise capacity (treadmill exercise duration,<sup>1–3</sup> maximal oxygen consumption (VO<sub>2</sub>),<sup>4–5</sup> and cardiac output<sup>6–7</sup>) and subjective assessment of symptoms by patients<sup>1–3</sup> are significantly improved by rate responsive pacing. Laboratory based exercise tests are, however, highly artificial and their clinical relevance has been questioned.<sup>8–9</sup> This has led to the development of corridor walk tests, which are considered to be a more natural way of assessing exercise capacity. Unsurprisingly, rate responsive pacing also improves exercise capacity using six<sup>10</sup> and 12<sup>11</sup> minute corridor walk tests. In spite of the fact that these tests are self paced their results correlate well with maximal VO<sub>2</sub> and they probably tell us little about patients' daily activity in their own homes.

Rate responsive pacing is assumed to improve daily activity in the home environment. In this study we investigate this assumption and compare the value of cardiovascular tests in patients receiving an established pacing technique of proven benefit.

## Methods

### PATIENTS

Twelve patients (mean (SD) age 59 (15) years) with VVIR units were recruited from the pacemaker clinic of a university hospital. All patients were pacemaker dependent. Table 1 lists their baseline characteristics and pacemaker details. Six had therapeutic AV nodal ablation for drug resistant atrial dysrhythmia. The mean (SD) time interval between pacemaker implantation and the study date was 22 (22.4) months. Pacemakers were

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Table 1 Patient and pacemaker characteristics

Case	Sex	Age	ECG rhythm	Aetiology	RR (range)	Activity threshold	Activity slope	Model
1	M	76	SR, CHB	Unknown	70–120	Medium	4	Senslog 2034T*
2	M	70	AF, CHB	IHD	70–130	High	4	Senslog 2034T*
3	M	68	PAF, CHB	Ablate	60–120	Medium	7	Legend 8416*
4	M	66	AF, CHB	Ablate	60–110	Medium	6	Senslog 2034T*
5	F	66	AF, CHB	Ablate	70–150	Low	11	Meta-3 1206†
6	F	29	AF, CHB	Ablate	80–150	Medium	7	Legend 8416*
7	M	33	SR, CHB	Congenital	60–100	–	15	Meta MV 1202†
8	M	56	SR, CHB	Congenital	70–120	Medium	7	Legend II 8427*
9	M	71	SR, CHB	Unknown	70–120	–	10	Opus G 4624*
10	M	61	SR, CHB	IHD	70–110	Medium	6	Excel VR 1120*
11	M	62	AF, CHB	Ablate	60–120	Medium	10	Thera SR 8940*
12	M	50	AF, CHB	Ablate	70–120	Medium	7	Thera SR 8940*

\*Activity sensor; †minute ventilation sensor.

RR, rate response; SR, sinus rhythm; PAF, paroxysmal atrial fibrillation; AF, atrial fibrillation; CHB, complete heart block; IHD, ischaemic heart disease; Ablate, nodal ablation.

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Table 2 Modified Bruce protocol

Stage	01	02	03	I	II
Stage duration (min)	4	3	4	3	4
Speed (km/h)	2.7	2.7	2.7	2.7	4.0
Slope°	0	1.3	2.6	4.3	5.4

optimally programmed according to the manufacturer's guidelines before entry to the study, and the activity slope was adjusted according to the patient's symptoms. The study was approved by the hospital ethics committee.

#### PACEMAKER PROGRAMMING AND STUDY DESIGN

Patients were randomly programmed to either predetermined VVIR or default VVI modes (table 1) for successive periods of one week in a single blind, crossover fashion. Programming was performed by a cardiac technician who was not involved in the study. Seven patients were initially programmed to VVI, and the remaining five to VVIR. The investigator could not be blinded as all exercise tests were performed with electrocardiogram monitoring. Early crossover to the next arm of the study was permitted at the patient's request.

#### MEASUREMENTS OF EXERCISE CAPACITY

##### Treadmill tests

There was an initial three week run in period during which symptom limited treadmill tests were performed in VVIR mode according to a modified Bruce protocol (table 2).

Patients breathed through a mouthpiece connected through a flow meter to a mixing box. Mass spectrometry (ESS Ltd, Cheshire, UK) was used to analyse the composition of inspired air from the inlet valve and mixed expired air from the mixing box for determination of oxygen uptake and carbon dioxide ( $\text{CO}_2$ ) production. Subjective assessment of exercise difficulty was made at the end of each stage using Borg scores.<sup>12</sup> Randomisation occurred when modified Bruce exercise times stabilised to within 5% of the previous test. Two additional treadmill tests were performed at randomisation: a submaximal (80%) modified Bruce test with measurements of cardiac output (see later) and a symptom limited fixed workload test (slope 4.3%, speed 2.7 km/h). The fixed workload test was terminated either at the patient's request on symptom limited exercise or after 30 minutes (whichever was sooner).

##### Estimation of cardiac output

Cardiac output was measured non-invasively by the indirect Fick method using  $\text{CO}_2$  as an indicator gas. Mass spectrometry was used to measure  $\text{CO}_2$  production, mean end tidal  $\text{CO}_2$  (equivalent to pulmonary venous  $\text{CO}_2$ ), and the plateau phase  $\text{CO}_2$  concentration following re-breathing into an anaesthetic bag (equivalent to pulmonary artery  $\text{CO}_2$ ). Measurements were made at rest and at 80% of the predetermined peak modified Bruce exercise time. We have previously validated this method against direct measurements of cardiac output by thermodilution.<sup>13</sup>

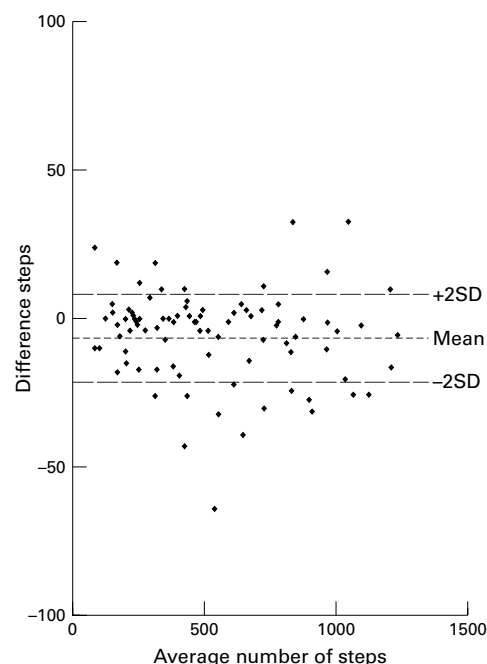


Figure 1 Bland and Altman plot showing measurement agreement between shoe pedometers and visual step counting. Six patients exercised at low, medium, and high levels of activity (arbitrarily defined as 2, 3, and 4 km/h, respectively) for 5, 10, 15, 20, and 25 minutes on the treadmill at zero incline. Steps were counted manually by an observer and using the shoe pedometers.  $\bar{x} = 7.8$  steps. Mean difference = -5.2 steps. Coefficient of variation 1.3%.

##### Corridor walk tests

These were performed over a distance of 100 m at self selected "slow", "normal", and "fast" speeds. Exercise times were recorded in seconds and the subjective level of difficulty was assessed using Borg scores.

#### DAILY ACTIVITY

Daily activity was measured using Digi-walker hip pedometers (Yamax, Yokohama, Japan) and electronic shoe pedometers contained within the sole of an everyday pair of shoes (Medical Physics Department, Queen's Medical Centre, Nottingham). Both have previously been validated as methods of step counting.<sup>14</sup> The hip pedometers were calibrated before and after every use to permit total foot fall to be estimated. Patients were instructed to wear the hip pedometers all day, every day for the seven days of each study arm.

Shoe pedometers were available only for male patients. Each pedometer consists of a transducer, a battery, and circuitry containing a memory chip and clock. The transducer is a flexible strip switch that exhibits decreasing resistance when a force is applied to its surface. The weight required to activate the transducer is about 2 kg. Pulses from the transducer are accepted or rejected according to a preset frequency window to eliminate false activation. The memory chip records the number of foot falls in every 20 second period for a total of seven days. The shoes are decoded by an external interface with a portable computer. Patients were instructed to wear the shoes all day (even when inactive indoors) for the seven days of

Table 3 Results of treadmill exercise tests in VVIR and VVI

	VVIR	VVI	p value
<i>Modified bruce exercise protocol</i>			
Exercise time (s)	1096 (45)	883 (60)	< 0.005
Work done (kJ)	41.2 (8.3)	21.0 (2.6)	< 0.05
Resting VO <sub>2</sub> (ml/min/kg)	3.7 (0.2)	3.5 (0.3)	NS
Peak VO <sub>2</sub> (ml/min/kg)	16.1 (1.2)	13.2 (0.9)	< 0.005
Rate pressure product	18010 (1138)	11354 (602)	< 0.005
Borg score at peak exercise	15.8 (0.5)	15.6 (0.7)	NS
Resting CI (l/min/m <sup>2</sup> )	1.9 (0.1)	1.9 (0.2)	NS
Submax CI (l/min/m <sup>2</sup> )	4.8 (0.3)	4.2 (0.3)	< 0.05
<i>High level exercise protocol</i>			
Exercise time (s)	1548 (132)	1359 (180)	< 0.05
Work done (kJ)	68.4 (0.3)	58.3 (0.4)	< 0.05
Peak VO <sub>2</sub> (ml/min/kg)	10.9 (0.3)	10.6 (0.4)	NS
Rate pressure product	14424 (977)	11269 (790)	< 0.05
Borg score at peak exercise	13.8 (1.1)	15.3 (1.0)	NS

Values are mean (SEM).

each study arm. Patients kept a diary of wearing so that total activity could be expressed as the average number of steps taken per hour worn. The results were also presented as the percentage of time worn during which the patient was active. The Bland and Altman plot (fig 1) shows measurement agreement (coefficient of variation 1.3%) between the shoe pedometers and the gold standard of visual step counting.

#### QUALITY OF LIFE ASSESSMENT

Quality of life (QOL) was assessed using a self administered, disease specific questionnaire. This questionnaire has been validated within our department and used in several multicentre studies of patients with cardiovascular disease.<sup>15 16</sup>

#### STATISTICAL ANALYSIS

All results are given as mean (SEM) values unless otherwise stated. Normal distributions were seen for peak VO<sub>2</sub> and cardiac index at submaximal exercise. The paired *t* test and the Wilcoxon signed rank test were used to assess the level of significance of differences between pairs of parametric and non-parametric numerical data. Observed differences were considered significant at *p* < 0.05.

### Results

#### TREADMILL EXERCISE TESTS

No patient was withdrawn from the study. Patient number 4 requested early crossover from VVI to VVIR. Table 3 shows significant improvements in VVIR using the modified Bruce and fixed workload protocols. Borg

scores at peak exercise were equivalent for VVI and VVIR during both the modified Bruce and fixed workload exercise protocols, indicating that the patients consistently exercised to equivalent levels of symptom limitation.

Mean (SEM) improvements in peak VO<sub>2</sub> (2.9 (0.8) *v* 0.3 (0.4) ml/min/kg, *p* < 0.05) and rate pressure product (6656 (1011) *v* 3155 (836), *p* < 0.005) were greater with the modified Bruce protocol than with the fixed workload protocol. There were no significant differences between the protocols according to improvements in either exercise time or work done.

#### CORRIDOR WALK TESTS

Clinical improvement between VVI and VVIR was not detected by corridor walk times at slow, normal, or fast speeds (table 4). However, measurement of self rated symptomatic impairment during exercise with Borg scores indicated that patients exercised with greater ease at their normal and fast speeds in VVIR (*p* < 0.05).

#### QUALITY OF LIFE SCORES

There was a mean overall improvement in QOL scores of 13% in VVIR (*p* < 0.05, table 4). There was no significant difference in QOL between baseline and VVIR.

#### DAILY ACTIVITY

Table 4 shows that switching from VVI to VVIR was not associated with improved daily activity measured using either belt or shoe pedometers.

### Discussion

Treadmill based exercise tests and self administered QOL questionnaires were effective tools for assessing the beneficial effect of VVIR pacing on exercise performance and patient symptoms. The modified Bruce protocol was marginally superior to the fixed workload protocol as seen in the significantly greater improvements in peak VO<sub>2</sub> and rate pressure product. This finding shows that it is important to match the design of an exercise protocol to the expected abilities of the study patients. The fixed workload protocol was too easy for our relatively fit and active patients; VO<sub>2</sub> reached a plateau during exercise in six patients in VVI, all of whom continued to exercise for the full 30 minute schedule.

Surprisingly, large improvements in treadmill based exercise capacity and patients' symptoms did not translate to improvements in daily activity. In this study, using shoe pedometers, 85% (steps/hour) and 90% (% of time active) power led to the detection of a 25% change in daily activity at a significance level of *p* < 0.05. These negative findings are unlikely to have arisen as a result of a type II error. Contrary to what was expected, an effective treatment (rate responsive pacing) failed to improve daily activity. This observation is similar to one that we have already made concerning vasodilator treatment in patients with mild to moderate heart failure.<sup>9</sup> The explanation for these observations is unclear, but may be related to patient selection. It is important to

Table 4 Results of corridor walk tests in VVIR and VVI

	VVIR	VVI	p value
<i>Corridor walk tests</i>			
Slow walking pace (s)	86.5 (2.6)	86.9 (3.0)	NS
Borg score	6.7 (0.3)	7.8 (0.7)	NS
Normal walking pace (s)	73.4 (2.1)	72.6 (2.0)	NS
Borg score	7.4 (0.5)	9.1 (0.8)	< 0.05
Fast walking pace (s)	59.6 (2.0)	61.9 (1.6)	NS
Borg score	8.9 (0.8)	12.5 (0.9)	< 0.05
<i>Quality of life (QOL)</i>			
QOL score (max 210)	181.8 (0.4)	161.5 (5.5)	< 0.05
<i>Customary activity</i>			
7 day score*	63687 (8572)	57941 (10404)	NS
Steps per hour†	578 (72)	516 (82)	NS
% of time active†	34.7 (4.4)	34.0 (4.4)	NS

Values are mean (SEM).

\*Hip worn pedometer data (steps per week); †shoe worn pedometer data.

realise that our patients were relatively fit and active. In spite of their underlying cardiovascular disease (as reflected by their reduced peak  $\text{VO}_2$ ) their level of daily activity was comparable to that for medically fit, young adults (70 000 steps/week).<sup>17</sup> Most people live their daily lives to ordered routines during which they rarely exercise maximally. It may be that unless a disease state severely limits exercise capacity, we should not expect a treatment to result in an improvement in daily activity. Furthermore, the results of the corridor walk test support the interpretation that although the addition of VVIR did not influence the level of daily activity, it did permit patients to exercise at the same level with fewer symptoms (as shown by the lower Borg scores in VVIR at normal and fast walking speeds).

Daily activity is an important measurement as it tells us something about what patients do in their real lives, as opposed to what they can do when they are "flogged" on a treadmill. Furthermore, in heart failure, reduced daily activity has been identified as an independent marker of poor prognosis.<sup>18</sup> Step counting is a sensible and easy method of assessing daily activity. Shoe pedometers are superior to belt pedometers as they directly measure foot fall rather than the tilting motion of the pelvis associated with walking, and incorporation of a timing device permits analysis of activity levels over the study period.

#### CONCLUSIONS

This study highlights the difficulties of selecting a test to measure clinical improvement in patients with symptomatic disease. The best way of evaluating exercise capacity is still unclear, possibly because it may vary according to aetiology and severity of the disease.

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